# Prenatal Megacystis - Is Prediction of Outcome and Renal Function Possible?

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# [i]Prenatal Megacystis – Is prediction of outcome and renal function possible?

## Introduction

Foetal megacystis is a rare but potentially curable foetal disease with a 9 to 1 male predominance. The cause is either morphological or functional obstruction of the foetal urethra. The main problem after prenatal detection of foetal megavesica is parental counselling as to the prognosis for the individual case. Up to now the decision for prenatal intervention is based mainly on urine analysis first reported by Glick and refined by Johnson 1995 using sequential vesicocentesis [1],[2]. Recent metaanalysis revealed that antenatal testing of renal function is of variable accuracy [3]. Case reports and small series have demonstrated that renal function cannot be predicted by fixed cut-offs of urine analysis alone. [4] [5], [6] [7]. Recent reports emphasise that besides urine electrolytes, osmolarity and beta-2-microglobuline renal sonomorphology and amount of amniotic fluid may be predictors for postnatal renal function [8], [9], [10]. Management options include vesicocentesis, vesicoamniotic shunting and operative foetal cystoscopy with laser ablation of urethral valves [11], [12], [3], [13]. Long-term outcome of foetuses treated with vesicoamniotic shunting for lower urinary tract obstruction is scarce [14], [15]. Systematic review of the effectiveness of antenatal intervention give limited evidence that intervention seems to improve perinatal outcome particularly in cases with predicted poor outcome [16]. A recent randomised controlled trial presented higher survival rates after vesicamniotic shunting, but due to poor recruitment the effect could not be proven and subgroup analysis was impossible [17].

In a recent paper, criteria for fetal interventions were presented on the basis of fetal urine biochemistry [18]

The aim of our study is to document the clinical experience of antenatal management of foetal megavesica and describe postnatal outcome in relation to antenatal test results in a series of consecutive patients cared for in one institution. This is a basis for parental counselling.

## Methods

In a retrospective study at the Department of Obstetrics, University Hospital Zurich and at the University Children's Hospital Zurich we describe prenatal management and the long-term outcome of foetal megavesica. From October 1995 till December 2008 53 cases of foetal megacystis were diagnosed at our tertiary referral centre. During this time period a total of 26'675 women gave birth at our institution which gives a prevalence for foetal megavesica of 0.2%. Recent data from a population-based epidemiological study gives prevalence rates of 3.34 per 10 000 births [19]. Therefore we are dealing with a highly selected population in a tertiary referral centre.

Gestational age at referral ranged from 12 to 34 weeks of gestation. The bladder size was measured by ultrasound in three planes from a transversal and longitudinal section of the foetus. The diagnosis of foetal megacystis in the first half of pregnancy was made, if the mean bladder diameter was more than 20mm. In this patient population spontaneous resolution is reported to be exceptional [20], [11]. During the second half of pregnancy in addition to increased bladder size, oligohydramnios according to the largest pocket method and dilatation of foetal renal pelvis must be present. The sonographic exams were performed using standard Ultrasound equipment (Acuson XP, Siemens Elegra and Voluson 730 Expert) by an experienced sonographer (J.W.).

If the inclusion criterion for megacystis was met, the patients were counselled as to the uncertain prognosis and diagnostic procedures were offered in order to clarify the situation. As a first step we offered vesicocentesis to evaluate urine electrolytes (sodium, chloride and calcium), urine osmolarity and urine β2-microglobulin as well as a cytogenetic examination of the foetus.

On the basis of the actual knowledge and published guidelines [1], [2] patients were counselled and decided either to proceed with pregnancy with repeated punctures or to opt for termination of pregnancy.

With the informed consent from the parents we collected data on the clinical course of these children and obtained data from a follow-up period of 2 to 12 years from the documents of the paediatrician. We documented the diagnostic and therapeutic procedures and the actual clinical situation with special interest in the creatinine levels. Kidney function was classified as normal or impaired according to serum creatinine values using sex and age-specific reference ranges [21].

Clinical follow-up and assessment of outcome was performed for all 15 patients who continued pregnancy and survived neonatal period.

In order to evaluate the prognostic values of urine analysis, we compared the values from the 10 surviving foetuses with prenatal vesicocentesis (one surviving female with trisomy 21 excluded) with 11 foetuses who died either pre- or postnatally without concomitant malformations. In cases of recurrent foetal vesicocentesis, the last available foetal urine sample was used for prognostic assessment.

Statistical analysis included logistic regression analysis and ROC curves calculation for the gestational age dependent variables β2-microglobulin, osmolarity and chloride in order to draw the discrimination line between survivors and non-survivors (cases after termination excluded). In addition the amount of amniotic fluid according to the deepest pocket method was correlated with postpartum renal function, applying Fisher's exact test to assess statistical significance.

## Results

The description of the study population is presented in Fig 1

From the total of 53 cases of megavesica 47 cases (88,7%) were diagnosed before and 6 cases (11,3%) after the 24$^{th}$ week of gestation.

In 43 of the 53 cases (81,1 %) vesicocentesis was performed. In three cases (5,6%) at 13, 14 and 16 weeks of gestation, megavesica resolved spontaneously before the procedure was performed. In 7 cases (13,2%) no vesicocentesis was performed either because of contraindication (maternal HIV-infection) or refusal of the parents.

The diagnostic examination included a cytogenetic evaluation in 47 out of 53 cases either from amniotic fluid or the evaluation of foetal urine. In 41 cases we found a normal karyotype, whereas 6 foetuses presented aneuploidies (three cases 47,XY + 13, two cases 47,XY + 18 and one case 47,XX + 21).

Termination of pregnancy was performed in 23 cases. 5 cases had an abnormal karyotype (trisomies 13 and 18). Pathological values of vesicocentesis, oligo- or ahydramnion and the wish of the parents were the reason for the remaining 18 cases. There were 3 (5.7 %) intrauterine foetal deaths and 12 children (22.6 %) died postnatally. (Figure 1)

Postnatal renal function of the 15 survivors was classified according to published age- and sex-related creatinine values into normal and impaired renal function (RF) [21]. Thereafter the children were grouped according to the necessary neonatal and paediatric treatment (Tab 1). 8 children survived with normal renal function whereas 7 presented with impaired renal function after operative interventions.

The prognostic value of amniotic fluid volume for the assessment of postnatal renal function is presented in the following Tab. 2 and summarized graphically in Fig. 2

Applying Fisher's exact test to data presented in Tab. 2 show that there is a significant association between normal amniotic fluid and normal renal function post partum and abnormal amniotic fluid with impaired renal function or perinatal death (PD) ($p = 0.0027$).

Logistic regression of urine β2-microglobulin (Fig. 3a), osmolarity (Fig.4a) and chloride (Fig. 5a) in relation to gestational age for the 10 survivors (foetus with trisomy 21

excluded) and 11 perinatal deaths (termination of pregnancy excluded) as well as corresponding ROC-curves (Fig. 3b, 4b, and 5b) are presented in the following graphs.

For β2-microglobulin Fig. 3 shows complete discrimination between survivors and non-survivors by the calculated gestational age dependant regression line.

For osmolarity and chloride the presented regression line show clinically helpful discrimination between the two groups and ROC-curves show area under the curve (AUC) of 0.81 and 0.76, respectively.

In the group of 11 surviving children with vesicocentesis, including the child with trisomy 21, prenatal urine analysis including β2-microglobulin, osmolarity and chloride does not discriminate between postnatal normal and impaired renal function. (Fig 6 a-c)

## Discussion:

Foetal megavesica is a rare condition with a prevalence of 0.06 % in screening population [22], whereas in our tertiary center the prevalence was 0.2% which is as high as previously described for referral centers [23]. The condition is potentially curable but published mortality rates in tertiary centers is high, with 15 out of 16 foetuses dying (93.8%) [23]. Actual data from the same institution show only 6 survivors out of 72 fetuses (8.3%) [18]. In a recent randomised controlled trial (PLUTO trial) only 31 out of 99 pregnancies were continued. Only ten children survived the 2-year period which gives a total mortality rate of 89.9% and a 64.5% mortality in ongoing pregnancies [17]. In our series 30 of 53 pregnancies continued after prenatal diagnosis. In 15 cases perinatal deaths occurred which gives a mortality of 50% for ongoing pregnancies and 71.7 % total mortality. We observed only 3 of 53 (5.7%) foetuses showed spontaneous remission whereas in another screening population

with less strict inclusion criteria, the spontaneous remission rate was 8 out of 15 (53.3%) [22]. These data show that besides our strict inclusion criteria for the diagnosis of fetal megavesica, the prognostic assessment in our patients is rather better than in the PLUTO trial and other published series.

8 of our 15 survivors had a normal renal function at a maximum of 12 years and a minimum of 2 years of age. The PLUTO trial reported only 2 out of 10 survivors with normal renal function whereas 7 children had moderate, and 1 end-stage renal function impairment.

Our study shows that in 6 out of 47 (12,8%) foetuses megavesica was associated with an abnormal karyotype. The prevalence and the spectrum of chromosomal anomalies is comparable to previously published data. In the largest series of foetuses with megavesica > 15mm during the first trimester, 4 out of 35 (11.4%) have a chromosomal anomaly [20]. Therefore, foetal karyotyping is a keystone in the prenatal evaluation of foetal megavesica.

Prenatal counselling as to the prognosis and the postnatal outcome is difficult and currently not based on profound scientific evidence. Our data confirm that renal function is associated with the amount of amniotic fluid. Reduced amniotic fluid has a significantly higher risk for impaired postnatal renal function and perinatal death compared to normal amniotic fluid. Another prognostic factor seems the sonomorphologic appearance of the foetal kidneys, which we could not evaluate in our retrospective study [8],[24]. However, using sonomorphology, one has to take into account the gestational age dependent changes of renal echogenicity.

The cornerstone for the estimation of foetal renal function is the assessment of urine biochemistry, originally described by Glick [3]. Various studies cast doubt on the fixed cut-off values proposed by Glick and instead described gestational age dependent reference curves for urine markers [25], [4], [18].

Our data show a gestational age-dependent discrimination line of foetal urine β2-microglobulin, which allows discrimination between survivors and perinatal deaths from the beginning of second trimester onwards. For foetal urine osmolarity and foetal urine chloride we presented a discrimination line between those two groups which is clinically helpful as shown in the ROC-curves.

Unfortunately, our data were unable to demonstrate (Fig.6) that foetal urine osmolarity and foetal urine β2-microglobulin can discriminate between postnatal normal or

impaired renal function. The graph suggests that low β2-microglobuline values during the first half of gestation seem to be associated with normal postnatal renal function. Only larger series can definitively clarify this issue.

According to our data and supported by previous work, a fixed cut-off level of foetal urine markers is not helpful in the counselling of parents with foetal megavesica. Furthermore, such fixed cut-offs are not helpful in decision-making for foetal invasive procedures. Therefore systematic reviews based on these parameters are far from being evidence based [16].

Prediction of outcome and renal function in foetuses with megacystis is still challenging. Implementing gestational age-dependent cut-off lines for foetal urine markers as described, may be helpful in patient counselling. In our set-up 23 out of 53 parents (43.4%) opted for termination of pregnancy (TOP), whereas is other series in tertiary centers the rate for TOP was 53 out of 72 (73.6%) fetuses.

In the literature, the determination of fetal urinary peptides using capillary electrophoresis coupled with mass spectrometry seems a promising approach to predict foetal prognosis [26]. The measurement of urinary gamma-glutamyl-transpeptidase (GGTP) can predict urodigestive fistulae [18].

In conclusion, our study shows that fetal urine analysis can discriminate between survivors and non-survivors with high reliability, when using gestational-age dependent regression lines for β2-microglobuline, osmolarity and chloride. Therefore, these data are important for parent counselling and as selection criteria for fetal interventions. In order to prove this concept of parent counselling the presented regression lines need to be assessed in prospective studies.

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